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Local Protocol #: IST-ASTX-SGI 110-MPN

Title: A phase II study of SGI-110 in Philadelphia-negative myeloproliferative neoplasms

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1. OBJECTIVES

1.1 Study Design: Open label single-arm, single-institution study to evaluate the efficacy and safety of SGI-110 in Philadelphia chromosome negative (Ph-) Myeloproliferative Neoplasms (excluding PV, ET and primary/secondary myelofibrosis). While this study would begin as a single institution study, it may be open later as a multi institutional study.

1.2 **Primary Objective:** Determine the efficacy of SGI-110 in improving hematological and/or quality of life outcomes in patients with Ph- MPN

1.3 Secondary Objectives:

Determine whether SGI-110 has increased efficacy in specific morphologic, cytogenetic and/or molecular subgroups of MPN

Perform correlative scientific studies to assess potential epigenetic or other biomarkers predictive of response

2. BACKGROUND

2.1 SGI-110

2.1.1 SGI-110 Background

For further information on SGI-110 please refer to the most up to date version of the Investigator's Brochure (IB).

The active metabolite of SGI-110 (2'-deoxy-5-azacytidylyl-(3'→5')-2'-deoxyguanosine sodium salt), a dinucleotide, is decitabine, an FDA-approved agent for the treatment of myelodysplastic syndromes. SGI-110 is resistant to modification by cytidine deaminase, a common pathway of decitabine metabolism and deactivation[1]. The molecular weight of SGI-110 and decitabine are 580 Da and 228 Da, respectively. Therefore, the molar equivalent dose of 1 mg of decitabine is approximately 2.5 mg of SGI-110. SGI-110's activity was demonstrated with the same preclinical pharmacodynamic assays used to demonstrate decitabine's efficacy e.g., re-expression of p15, p16, and MLH1 and induction of fetal hemoglobin, *in vivo*. In xenograft studies, SGI-110 demonstrates promising preclinical activity in both hematologic and solid tumors.

In vitro evidence suggests that SGI-110 has a longer half-life than decitabine in the presence of cytidine deaminase. These promising observations suggest that SGI-110 may have improved pharmaceutical properties and biological activities that could extend decitabine's current clinical utility. SGI-110 has shown to be better tolerated in mice than decitabine and is as effective *in vivo* in inducing p16 expression, reducing DNA methylation at the p16 promoter region, and retarding EJ6 human bladder cancer tumor growth in athymic mice[2].

SGI-110 has been developed for subcutaneous administration. SGI-110 is pharmacologically active both *in vitro* and *in vivo* in a variety of tumor cells and murine xenograft models when administered subcutaneously. Treatment is well tolerated via the subcutaneous route in murine xenografts. When administered subcutaneously to non-human primates, SGI-110 releases decitabine slowly compared to other species, possibly prolonging the effect over longer periods. SGI-110 has been developed as a non-aqueous formulation to ensure formulation stability.

2.1.2 Nonclinical pharmacokinetics

The overall pharmacokinetic characteristics of SGI-110 are summarized as follows. The relative bioavailability of SGI-110 dosed subcutaneously in rats is close to 100%. Circulating SGI-110 levels were very low in the mice, rats and rabbits. However, higher levels were observed in monkeys post subcutaneous dosing. Rapid decline in systemic exposure of SGI-110 with elimination plasma half-life (T1/2) in the range of 0.4-1 hours in rats and monkeys was observed. High levels of decitabine were observed after a subcutaneous dose of SGI-110 in mice, rats, and rabbits (maximum in rat, 54 μg/mL). Levels in monkeys (maximum 463 ng/mL) were substantially lower. Rapid decline in systemic exposure of decitabine with elimination plasma $T_{1/2}$ of 3.7 hour in rats and 1 hour in monkeys was observed.

In monkeys, pharmacokinetic parameters were similar on Day 1 and Day 15 of a study in which they were dosed once weekly for three consecutive weeks suggesting no significant accumulation of the parent or the active metabolite, decitabine.

The metabolic characteristics of SGI-110 are summarized as follows. SGI-110 was more stable in humans, dogs and mice and was less stable in rats and rabbit plasma. Incubation of SGI-110 with liver microsomes from mouse, rats, rabbits, dogs and humans showed little apparent metabolism of the compound. Incubation of SGI-110 with human hepatocytes also showed little apparent metabolism of the compound, based on disappearance of the parent. SGI-110 does not significantly bind to human plasma proteins; *in vitro* unbound fraction was estimated to be 91%. SGI-110 has poor *in vitro* bidirectional permeability which correlates well with its poor oral absorption *in vivo*. SGI-110 shows no appreciable induction of CYP1A1/2, CYP2C9 and CYP3A4 in human hepatocytes. SGI-110 does not have any CYP450 inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

2.1.4 Nonclinical safety of SGI-110

SGI-110 toxicity findings in rat and rabbit studies are similar to the non-clinical study findings of decitabine in New Drug Application (NDA) supporting Good Laboratory Practices (GLP) toxicology studies. Myelosuppression, decreases in thymus weight, and testicular atrophy, the main study findings of the SGI-110 studies, were also observed as the main study findings in repeat dose toxicity studies with decitabine in mice, rats, rabbits, and dogs. As with SGI-110, myelosuppression and thymus toxicities after decitabine administration were reversible during recovery periods while testicular atrophy persisted. Myelosuppression, particularly neutropenia, has been reported as a dose-limiting toxicity for decitabine in human clinical studies. Signs of

testicular toxicity have not been observed in any of the published clinical studies of decitabine to date.

No studies have been performed to evaluate the genotoxic, mutagenic, carcinogenic or reproductive and developmental toxicity of SGI-110. Decitabine may have genotoxic potential; decitabine is mutagenic and in preclinical studies in mice and rats, decitabine was teratogenic, fetotoxic, and embryotoxic.

2.1.5 SGI-110 Clinical Data

SGI-110 has been studied in a first-in-human, single-agent study (SGI-110-01).[5] This study was a Phase 1/2, dose escalation, multicenter study of two subcutaneous regimens of SGI-110 in subjects with intermediate or high-risk myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML). This study had two parts, a Dose Escalation Segment and a Dose Expansion Segment. The study evaluated the biological activity, preliminary safety, and efficacy of SGI-110 with two dosing schedules in intermediate to high risk MDS or relapsed or refractory AML subjects, while the Dose Expansion Segment further evaluated safety and efficacy at the recommended dose. The study was based on a 3 + 3 design within each regimen. Eligible subjects were randomized to receive 1 of 2 dosing regimens of SGI-110 with the following starting doses: Regimen 1: 3 mg/m^2/day subcutaneously on Days 1-5 of a 28-day course, Regimen 2: 6 mg/m^2 subcutaneously Weekly x 3 on Days 1, 8, 15 of a 28-day course. The minimum dose achieving maximal biological activity or biologically effective dose (BED) for the daily regimen was reached at 60 mg/m^2 daily on Days 1-5.

2.1.6 Human pharmacokinetics

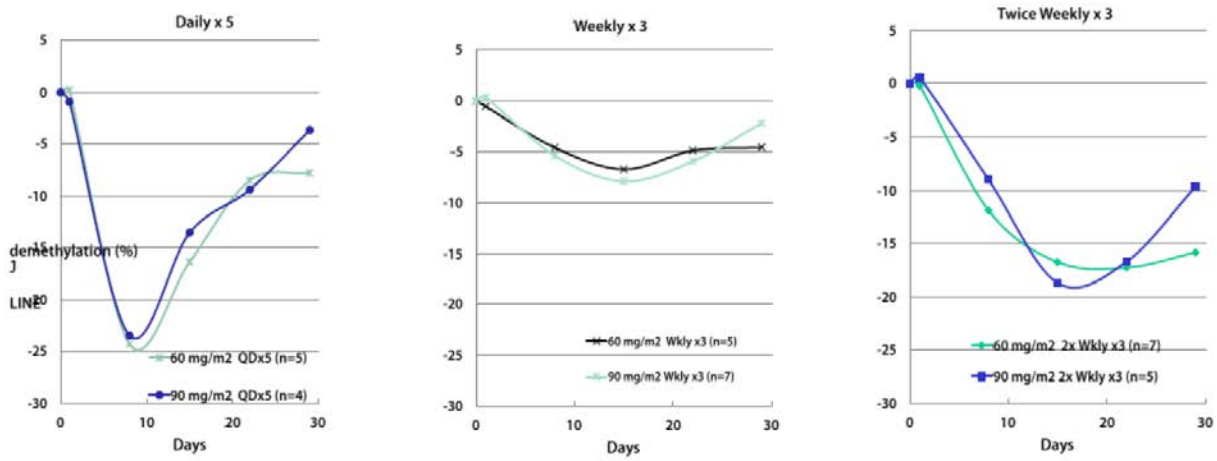
The PK of SGI-110 and decitabine are being evaluated in Study SGI-110-01. Decitabine forms from SGI-110 as it undergoes cleavage by phosphodiesterase (PDE) enzymes. SGI-110 after SC injection undergoes efficient conversion to decitabine and delivers decitabine exposures as measured by AUC that are equivalent or higher than those achieved by IV decitabine infusion at 20 mg/m^2, while maintaining significantly lower decitabine C_{max}. It is hypothesized that lower C_{max} may be associated with less toxicity.

Due to slower release of decitabine from SGI-110, the effective half-life of decitabine after SC SGI-110 is prolonged and the observed decitabine exposure window is longer (8+ hrs) compared to IV (3-4 hrs). At Cohort 6, doses of 90 mg/m^2 for the daily regimen and 125 mg/m^2 for weekly, the observed decitabine AUCs were approximately 1.41 and 1.77 fold higher than with IV decitabine at the approved dose of 20 mg/m^2 IV, whereas C_{max} levels were only at 0.35 and 0.44-fold for the daily and weekly regimens, respectively. It is hypothesized that longer exposure to decitabine may allow more drug to be incorporated into the DNA thus resulting in better hypomethylation and better biological activity. Clinical drug-drug interaction studies have not been conducted with SGI-110. *In vitro*, SGI-110 does not inhibit the activity nor induce levels of major human CYP enzymes, hence, the likelihood of CYP-mediated drug-drug interactions with SGI-110 is remote.

2.1.7 Clinical efficacy and biological activity of SGI-110

Based on PD assessment of global hypomethylation from the first 7 cohorts in Study SGI-110-01 Dose Escalation Segment, the LINE-1 demethylation data show dose dependent hypomethylation induction in the daily schedule reaching a plateau at 60 mg/m^2 SC dailyx5. The hypomethylation of the weekly schedule was inferior to the daily schedule and plateaued early (Figure 1). The Biologically Effective Dose or BED was therefore established as 60 mg/m^2 dailyx5.

Figure 1: LINE-1 Demethylation



There have been 5 documented major responses (2 CRs and 2 CRi, 1 CRp) all in heavily-pretreated refractory AML subjects regardless of prior hypomethylating agents (HMA) treatment : 1 CR and CRp with weekly (60 mg/m^2 and 125mg/m^2, respectively) and 2 CRi and 1 CR with daily (36/60 mg/m^2 and 60 mg/m^2 respectively). The major responses were observed in 5/19 refractory AML patients when adequate hypomethylation (>10%) was achieved. Five MDS patients who all received prior treatment with HMAs had hematological improvements or marrow CR. Since these initial data were reported, SGI-110 has shown further responses in patients with MDS and acute myeloid leukemia, phase II data have been reported and the agent is currently being tested in a phase III trial compared to decitabine in older patients with acute myeloid leukemia.

2.4 Study disease: MPN

Philadelphia chromosome negative Myeloproliferative Neoplasms (PHN-MPN) comprise a group of myeloid neoplasms with varying clinical, morphologic and laboratory features and a wide range of survival. According to 2008 World Health Organization (WHO) classification, the MDS/MPN overlap syndromes include chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia(JMML) and myelodysplastic/myeloproliferative neoplasm unclassifiable (MDS/MPN-U). In a recent retrospective study from MD Anderson Cancer Center, the median survival of patients with a

diagnosis of MDS/MPN unclassifiable was 12.4 months[3] .There is no effective therapy for PHN-MPN and this represents an unmet medical need.

The MDS/MPN overlap syndromes can present with a wide range of hematological and clinical manifestations and individual patients may exhibit a combination of features characteristic of both MDS and MPN. For example, while transfusion-dependent anemia is generally present, other hematological laboratory abnormalities can range from leukopenia to leukocytosis and from thrombocytopenia to thrombocytosis. Unlike with MDS, significant splenomegaly is often present in patients with PHN-MPN. Also, patients may have a constellation of constitutional findings, including fatigue, weight loss, anorexia, night sweats and other unpleasant symptoms that lead generally to poor quality of life. Thus, while improving overall survival is a critical goal of therapy, effective therapy for this group of patients will include also agents that can be demonstrated to improve as many of the disease-related clinical issues as possible.

2.5 Rationale

2.5.1 Both decitabine and SGI-110 have demonstrated safety and efficacy in patients with MDS, AML and CMML. Based on these data, substantial clinical experience and the lack of an effective treatment option in PHN-MPN, we hypothesize that treatment with SGI-110 will result in improved hematological and quality of life outcomes in patients with these diseases. SGI-110 will be administered subcutaneously at the dose level of 60mg/m^2 for 5 days to be repeated every 28 days. If the treating physician feels that SGI-110 needs to be started before 28 days for subsequent cycles, SGI-110 can be started before the 28 days in those clinical situations after getting permission from the study PI. To capture the potential ability of SGI-110 to improve both hematological and QOL measures, we will utilize a recently published composite endpoint for response assessement based on IWG-MDS, IWG-myelofibrosis and MFSAF (Myeloproliferative Neoplasm Symptom Assessment Form) tools: Savona et al., An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood*,125(12):1857-65.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have confirmed diagnosis of Philadelphia chromosome negative MPN neoplasm based on WHO classification [5] including Chronic Neutrophilic Leukemia (CNL), atypical Chronic Myeloid Leukemia (aCML), Chronic Myelomonocytic Leukemia (CMML), Myelodysplastic/myeloproliferative

neoplasm unclassifiable , accelerated phase myelofibrosis and MPN unclassifiable (defined as peripheral and or bone marrow blasts of 10-19%). Patients with early stages of Polycythemia Vera or Essential Thrombocytosis will be excluded from the study.

3.1.2 Age minimum of 18 years.

Because no dosing or adverse event data are currently available on the use of SGI-110 in participants <18 years of age, children are excluded from this study but may be eligible for future pediatric trials.

3.1.3 ECOG performance status ≤3

3.1.4 Participants must have normal organ function as defined below:

- Total bilirubin < or = 1.5 X institutional upper limit of normal unless attributable to underlying disease, hemolysis or documented Gilbert's syndrome
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal unless attributable to underlying disease
- Creatinine < 1.5add < or = 1.5X institutional upper limit of normal or creatinine clearance add using Cockcroft Gault ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.
- LVEF < 40 % is allowed as long as there is no NY class III/IV heart failure or uncontrolled arrhythmias.

3.1.5 The effects of SGI-110 on the developing human fetus are unknown. For this reason and because oncological agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Participants who have had any chemotherapy (investigational or FDA approved) (hydroxyurea is permitted) or radiotherapy within 2 weeks prior to study entry or

those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.

3.2.2 Participants may not be treated with any other investigational agents while on this study unless approved by the principal investigator AND the sponsors of BOTH investigational agents.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to decitabine or SGI-110.

3.2.4 Uncontrolled intercurrent illness including, but not limited to, infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
Pregnant women are excluded from this study because SGI-110 is a hypomethylating agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with SGI-110, breastfeeding should be discontinued.

3.2.5 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 3 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at Weill Cornell Medical College by the Lead Study Coordinator. A record of patients who fail to meet entry criteria (*i.e.* screen failures) will be maintained. Patient consent must be obtained prior to performing any study-related activities and registration must be completed prior to treatment.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled.

4.2 Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and sent to the Weill Cornell Medical College Joint Clinical Trials Office (JCTO). Email the following documents to the JCTO regulatory coordinator:

- Signed patient consent form
- HIPAA authorization form
- WCMC registration form
- Eligibility Checklist signed and dated by investigator and research nurse/study coordinator
- Source documentation to confirm eligibility, including pathology disease confirmation
- Documentation of any granted eligibility waivers

4.3 Patient assignment

Each subject who satisfies the eligibility criteria and is accepted for the study will be assigned a unique identification number. The subject number will be used to identify the subject throughout the study and will be entered on all study documents. Once the subject identification number has been assigned, a confirmation email will be sent to all site personnel.

This is an open-label study. There will be no blinding of treatment assignment.

5. TREATMENT PLAN

5.1 Overall Study Design

This is a single arm, open-label study of SGI-110 in patients with MPN.
SGI-110 will be administered subcutaneously at a dose of 60 mg/m^2 on days 1-5, repeated every 28 days. Toxicity will be evaluated using the NCI Common Terminology Criteria for Adverse Events Active Version 4. The frequency of toxicities per organ system will be tabulated using descriptive statistics. All patients who receive any amount of the study drug will be evaluable for toxicity.

5.2 Screening and pre-treatment criteria

5.2.1 Screening Procedures

Screening procedures and tests will be performed within 14 days before treatment administration with the exception of informed consent, bone marrow biopsy which may be performed within 28 days of the first dose of study drug.

- Provision of written informed consent. The ICF must be signed and dated by the subjects before collection of any samples or performance of any study-specific evaluations.
- Complete medical history, including demographics (date of birth, sex, race). A disease history, including the date of initial diagnosis and list of prior treatments and responses to these treatments, also will be recorded. Concurrent medical signs and symptoms must be documented to establish baseline conditions.
- Record concomitant medications.
- Record all study-procedure related AEs from the time of informed consent and then treatment-emergent AEs after the start of study drug administration (Course 1, Day 1) through 30 days after the last dose of study drug.
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.
- Complete physical exam including weight and examination
- Vital signs include resting systolic/diastolic blood pressure, resting heart rate, resting respiration rate, body temperature and pulse oximetry. Assess after the subject has rested in the sitting position for at least three minutes.
- ECOG performance status.
- 12-lead ECG (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, and QT/QTc (QtcF), morphology and overall interpretation**).**
- Height.
- Sample collection for clinical laboratory tests (hematology, chemistry and urinalysis).
- Serum or urine pregnancy test: for female subjects of child-bearing potential only. Results must be negative for the subject to be eligible for enrollment into the study.

5.3 Agent Administration

5.3.1 **SGI-110**

- SGI-110 administered at dose level of 60 mg/m^2 SC daily on Days 1-5 of a 28-day cycle. However, treatment delays are allowed per section 6.3.1

SGI-110 is administered by SC injection preferably in the abdominal area. The total amount (in mg) of SGI-110 to be administered will be determined based on the body surface area (BSA). In calculating the BSA, actual heights and weights should be used. There will be no adjustments to "ideal" body weight. The institutional standard for calculating BSA is acceptable. Dose adjustment should be made for a +/- 10% weight change at the beginning of each cycle

The site(s) of SGI-110 SC injections will be captured on the dosing CRF.

Investigators are prohibited from supplying SGI-110 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as sub-investigators on Food and Drug Administration (FDA) Form 1572. The investigator must ensure that subjects receive SGI-110 only from personnel who fully understand the procedures for administering the study treatment.

5.4 General Concomitant Medication and Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the subject records and on the appropriate case report form. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms (including antiemetics for nausea and vomiting, anti-diarrheals for diarrhea and anti-pyretics and anti-histamines for drug fever). All supportive measures for optimal medical care will be given during the period of study.

5.5.1 **Antibiotics**

Antibiotics may be utilized to prevent or manage febrile neutropenia based on institutional standard practice. Febrile neutropenia is defined as temperature at least 38.5ºC when the ANC is < 1000 µL. Febrile subjects should be evaluated by physical examination, complete blood count (CBC) with differential, and blood culture. Subjects with febrile neutropenia or suspected sepsis on the basis of the physical examination are to be hospitalized for appropriate broad spectrum antibiotic coverage, consistent with local pathogen sensitivities.

5.4.2 **Hematopoietic Growth Factors**

Granulocyte-colony stimulating factor (GCSF) may be administered per ASCO guidelines.[25] Use of other white blood cell stimulating factors after Course 1 can be employed according to accepted

practice or institutional guidelines, at the discretion of the treating physician. RBC transfusions can be administered at the discretion of the treating physician.

5.4.3 Prohibited Medications

The administration of any other anticancer agents including chemotherapy and biologic agents is NOT permitted, with the exception of hydroxyurea. Similarly, the use of other concurrent investigational drugs is not allowed unless specific approval has been obtained from the principal investigator AND the sponsors of BOTH investigational products. Red cell and platelet stimulating agents are not allowed on protocol. In life threatening situations, these can be given after permission from study PI.

5.5 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression to acute leukemia unless, in the opinion of the principal investigator, the subject is experiencing clinical benefit from SGI-110 despite laboratory evidence of progression to acute leukemia.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.6 Duration of Follow Up

Participants will be followed monthly for six months after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Post-study case report forms will capture information including subsequent treatments, response to subsequent therapy, and survival.

5.7 Criteria for Removal from Study Treatment

Participants will be removed from study treatment for:

- Unacceptable adverse events that the in the opinion of the investigator is harmful to the participant
- Violation of the study plan or for administrative and/or other safety reason after discussion with the sponsor

- Progression to Acute Myeloid Leukemia unless patient is deriving clinical benefit and it is in the opinion of the treating physician that the subject continue on the drug after discussion with the study PI.
- Progression of underlying disease (without transformation to AML) as specified in table 3.

The reason for study removal and the date the participant was removed must be documented. Alternative care options will be discussed with the participant.

When a subject discontinues/withdraws prior to study completion, all applicable activities for the final study visit should be performed at the time of discontinuation (after 28 days from last day or drug administration or before starting alternative treatment, whichever happens first). Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed.

If a patient withdraws for non-medical reasons the following procedures will be followed:

- Physical examination will be performed.
- Safety assessment (physical examination, vital signs, hematology and serum chemistry), performed 30 days after last treatment

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE).

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheal, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

6.1.1 Adverse Event List(s) for SGI-110

The most common AEs suspected by the investigators in Study SGI-110-01 to be related to the drug and observed to date in the MDS/AML population are: injection site pain, fatigue, nausea, thrombocytopenia, anemia and diarrhea. Based on the mechanism of action of the drug and its active form decitabine, myelosuppression (neutropenia, thrombocytopenia, and anemia) and the related consequences such as

infection (e.g. pneumonia), sepsis, and bleeding are the most likely risks for the drug. Mucositis has also been reported.

Pain and burning at the injection site has been reported that are related to dose and volume of injection as well as the speed of injection. Care must be taken to avoid intradermal injection**.** Ice packs will be applied prior to injection of SGI-110 and the drug will be injected slowly, over 30-60 seconds. If the injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pre-treatment with topical or systemic analgesics can be considered.

6.2 Dose Modifications for adverse events

All adverse events should be reported and considered as part of the overall safety evaluation of SGI-110. The Investigator should try to the best of his/her ability to assess whether an adverse event is related or unrelated to SGI-110. Dose modifications are not required for hematologic toxicities, but may be considered at the investigator's discretion, in collaboration with the Sponsor. In general, SGI-110 should be held for any:

1. Grade ≥ 3 non-hematologic toxicity (except nausea/vomiting, diarrhea) that fails to resolve to < grade 2 within 72 hours despite appropriate management.

2. Persistent grade ≥ 3 neutropenia or thrombocytopenia beyond day 56 of cycle 1 in the setting of a hypocellular bone marrow biopsy and absence of residual disease

3. Other clinically significant adverse event which, in the opinion of the Safety Review Committee (SRC), would place subjects at undue safety risk.

After resolution of toxicity, treatment with SGI-110 may be resumed at dose level of 45 mg/m$^{2.}$ Retreatment at the original dose level may be considered, depending on the nature of the AE, and after discussion with the principal investigator. If the same toxicity that led to the dose reduction occurs again at this dose level, SGI 110 can be resumed at 30mg/m^2 after the toxicity has resolved to Grade ≤ 2 or baseline levels. Missed doses will be replaced at the investigator's discretion. Dose modifications for drug-related hematological toxicities will be managed on a case-by-case basis, depending on the patient's disease status and response to growth factor support, in collaboration with theprincipal investigator**.** There is no mandatory dose reduction or delay for hematological toxicity, but delays up to 14 days and dose reductions down to 30 mg/m^2 will be permitted depending on clinical circumstances, after discussion with the principal investigator. Additional delays or dose reductions may be considered after discussion with the principal investigator at Weill Cornell Medical Center.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 SGI-110

7.1.1 **Description**

Sodium (2*R*,3*S*,5*R*)-5-(4-amino-2-oxo-1,3,5-triazin-1(2*H*)-yl)-2 (hydroxymethyl) tetrahydrofuran-3-yl ((2*R*,3*S*,5*R*)-5-(2-amino-6-oxo-1*H*-purin-9(6*H*)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate

7.1.2 **Form**

SGI-110 product is supplied in a two-vial configuration.

SGI-110 for Injection, 100 mg is a 5 mL glass vial containing lyophilized SGI-110 drug powder for reconstitution and subcutaneous injection using the custom diluent supplied in a separate vial. Each vial is stoppered with fluropolymer coated butyl rubber closure and sealed with a blue flip-off cap. *SGI-110 for Injection, 100 mg* vial is individually packaged in a heat-sealed aluminum foil pouch with a single desiccant bag to protect from moisture.

SGI-110 Diluent for Reconstitution, 3 mL is a 5 mL glass vial with 3 mL of custom diluent. Each vial is stoppered with fluropolymer coated butyl rubber closure and sealed with a white flip-off cap.

7.1.3 **Storage and Stability**

SGI-110 for Injection, 100 mg vial is stored at refrigerated condition of 2–8ºC in the original packaging until use. *SGI-110 Diluent for Reconstitution, 3 mL* can be stored at 2–30ºC in upright position until use. Both vials are preservative free and for single use only. SGI-110 must be stored in a secure, locked facility accessible only to authorized study personnel.

OSHA Guidelines for handling cytotoxic drugs outlined in the American Journal of Hospital Pharmacy must be followed.[22] As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of SGI-110. The use of gloves and protective garments is recommended. Preparation should occur in a vertical laminar flow biological hood using proper aseptic technique. If SGI-110 contacts the skin, it should be immediately be treated with borax buffer solution pH 10 followed by washing immediately and thoroughly with soap and water. If SGI-110 contacts the mucous membranes, flush thoroughly with water.

Drug spilling can be inactivated by 2 N sodium hydroxide solution.

7.1.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.1.5 **Availability**

SGI-110 is an investigational agent and will be supplied free-of-charge from Astex Pharmaceuticals.

7.1.6 **Ordering and accountability**

An initial supply of SGI-110 will be shipped to the investigational pharmacy when all the initiation documents, including IRB approvals and IRB approved ICF, have been received and reviewed by Astex Pharmaceuticals. Thereafter, it is the responsibility of the trial pharmacist to order a resupply.

SGI-110 must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other study center personnel supply SGI-110 to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol.

An accurate accounting of the study drugs and investigational devices must be maintained. These records must show dates, lot numbers, quantities received, dispensed, and returned and must be available for monitoring. SGI-110 accountability records must be maintained and readily available for inspection by regulatory authorities at any time.

7.1.7 **Destruction and Return**

At the end of the study, unused supplies of SGI-110 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. CORRELATIVE/SPECIAL STUDIES

Bone marrow aspirate and peripheral blood will be collected for correlative scientific studies at the time of routine study assessments as detailed in the study calendar. Experimental work will be performed in the laboratories of Monica Guzman, Ph.D. and Joseph Scandura, M.D, Ph.D. The samples would consist of peripheral blood and bone marrow aspirate. Approximately 10mL of bone marrow aspirate (in a syringe with heparin) and up to 20mL of peripheral blood in purple or green top tubes will be collected at time points as indicated in the study calendar. The study samples will be stored indefinitely unless the study participant requests in writing that the study samples be destroyed.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 2-week prior to start of protocol therapy with the exception of informed consent and bone marrow biopsy which may be performed within 28 days of first dose of study drug. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 5 days of the protocol-specified date, unless otherwise noted.

Assessment	**Screening**	**Course 1 Day 1 (+/- 5 days)**	**Course 1 Day 14 (+/- 5 days)**	**Course ≥ 2 Day 1 (+/- 5 days)**	**Course ≥ 2 Day 14 (+/- 5 days)**	**Final Safety Evaluation Visit (28 days +2 after last study drug)**
Physical examination[1]	X	X	X	X	X	X
Vital signs[2]	X	X	X	X	X	X
CBC including manual differential	X	X		X	X	X
Blood chemistry[8]	X	X	X	X	X	X
Urinalysis	X					X
ECG[3]	X					X
LVEF[4]	X					
Concomitant medication/non-drug therapies	X	X	X	X	X	X
Bone marrow aspiration or biopsy[5]	X					X
Adverse events		X	X	X	X	X
Spleen measurement[6]	X					X
QOL measurements[7]		X		X		X
Research Studies (bone marrow aspirate, peripheral blood) [9]	X		Xpb	Xpb		

1. Examinations will include assessment of extramedullary disease.
2. Vital signs will include weight, body surface area, body temperature (°C), pulse rate, and systolic and diastolic blood pressures.
3. Single ECGs will be obtained prior to first cycle only, repeat measurements based on clinical indication
4. Echocardiography or MUGA to be performed at baseline and repeated based on clinical indication. The same method that was used for Baseline LVEF determination will be used on repeat measurements.
5. Bone marrow samples will only be taken at baseline and the end of each cycle 3, 6 and 12. A confirmatory bone marrow will be needed 1 month after a CR/CRp is first detected by peripheral blood assessment confusing. Cytogenetics and molecular markers will be assessed only if a CR/CRp is obtained. Molecular marker assessment may be omitted if no molecular markers were detected at screening. Cytogenetics, immunophenotype and molecular markers may be obtained from the peripheral blood in the event of a dry tap.
6. Spleen size will be measured at baseline using US, MRI or CT at baseline and the end of cycle 3, 6 and 12. The same modality of imaging that was used at baseline will be used will be used for subsequent measurements **(IF NO SPLENOMEGALY PRESENT AT BASELINE EXAM AND NO SPLENOMEGALY ON PHYSICAL EXAM, US, MRI, CT MAY BE OMITTED AT SUBSEQUENT TIMEPOINTS)**
7. QOL measurements will be done using MFSAF scores at baseline and at beginning of every cycle.
8. Blood chemistry includes comprehensive metabolic panel, magnesium, phosphorus and uric acid, LDH
9. Research studies sample to be collected at baseline (Bone marrow) and day 14 of cycle 1 and then day 1 prior to each cycle from peripheral blood (pb). Research study samples from bone marrow (b) to be collected at the end of cycle 3, 6 and 12 as well as at the time of CR/CRp if the bone marrow biopsy is done outside the scheduled bone marrow biopsies per study guidelines.

10. MEASUREMENT OF EFFECT

As epigenetic agents may take many months to show their benefit as seen in MDS/AML studies, subjects receiving SGI-110 may continue receiving their assigned treatment if their disease progresses to leukemia or progression as discerned by the clinical investigator criteria if 1) the patient is clinically stable, 2) the patient is informed of their clinical results and agrees to continue therapy, and 3) the patient provider agrees that remaining on study would be appropriate for the patient.

10.1.1 Response Criteria: from Savona et al., An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood*,125(12):1857-65.

• **CR (presence of all of the following improvements)***
• Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
• Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)†
• Peripheral blood‡
• WBC ≤10 × 10^9 cells/L
• Hgb ≥11 g/dL
• Platelets ≥100 × 10^9/L; ≤450 × 10^9/L
• Neutrophils ≥1.0 × 10^9/L
• Blasts 0%
• Neutrophil precursors reduced to ≤ 2%
• Monocytes ≤1 × 10^9/L
• Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
• Provisional category of CR with resolution of symptoms:‡ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
• Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*
• **Complete cytogenetic remission**
• Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH§
• **Partial remission**
• Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity *except* in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
• **Marrow response**
• Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.

• Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart
• **Clinical benefit**
• Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 wk) to be considered a clinical benefit
• Erythroid response
• Hgb increase by ≥2.0 g/dL
• TI for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
• Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation‖
• Platelet response
• Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk
• Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
• Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L‖
• Neutrophil response
• Pretreatment ≤0.5 × 10^9/L at least 100% increase and an absolute increase ≥0.5 × 10^9/L
• Pretreatment, >0.5 × 10^9/L and ≤1.0 × 10^9/L At least 50% increase and an absolute increase ≥0.5 × 10^9/L‖
• Spleen response
• Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
• Symptom response
• Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit.¶

↲* Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

↲† If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.67

↲‡ Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.

↲§ Loss of cytogenetic burden of disease by (via FISH or classic

karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

↲|| Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 wk. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤10 × 10^9 cells/L but ≥1.5 × 10^9/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤2-3%) and/or 1 × 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

•

• **Table 3** Proposed criteria for measurement of disease progression in adult MDS/MPN

• **Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list**
• **Major criteria**
• Increase in blast count*
• <5% blasts: ≥50% increase and to >5% blasts
• 5-10% blasts: ≥50% increase and to >10% blasts
• 10-20% blasts: ≥50% increase and to >20% blasts
• 20-30% blasts: ≥50% increase and to >30% blasts†
• Evidence of cytogenetic evolution‡
• Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
• Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping
• New extramedullary disease
• Worsening splenomegaly
• Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at >5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable

distance for baseline splenomegaly of >10 cm
• Extramedullary disease outside of the spleen
• To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
• **Minor criteria**
• Transfusion dependence§
• Significant loss of maximal response on cytopenias ≥50% decrement from maximum remission/response in granulocytes or platelets
• Reduction in Hgb by ≥1.5g/dL from best response or from baseline as noted on complete blood count
• Increasing symptoms as noted by increase in ≥50% as per the MPN-SAF TSS‖
• Evidence of clonal evolution (molecular)¶

↵* Blasts as measured from the bone marrow.

↵† Patients with development of acute myeloid leukemia from MDS/MPN; 20-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.

↵‡ Increase in cytogenetic burden of disease by ≥50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.

↵§ Transfusion dependency is defined by a history of at least 2 U of red blood cell transfusions in the past month for a hemoglobin level <8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias resulting from therapy should not be considered in assessment of progression.

↵‖ MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

↵¶ The identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation; we suggest that this criterion should be used conservatively based on current evidence.

Myelofibrosis Symptom Assessment Form (MF-SAF) [4]

	Symptom	1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable
Fatigue (Brief Fatigue Inventory)	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW	0 (No Fatigue) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL Level of fatigue during past 24 hours	0 (No Fatigue) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	0 (No Fatigue) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
	Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your	
	• General Activity	0 (Does not Interfere) 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
	• Mood	0 (Does not Interfere) 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
	• Walking ability	0 (Does not Interfere) 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
	• Normal Work (includes work both outside the home and daily chores)	0 (Does not Interfere) 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
	• Relations with other people	0 (Does not Interfere) 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
	• Enjoyment of life	0 (Does not Interfere) 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)

Splenomegaly and associated mechanical symptoms	Filling up quickly when you eat (Early Satiety)	Examples	0 (Absent) 1 2 3 *Does not limit how much you can eat*	4 5 6 7 *Moderately limits how much you can eat*	8 9 10 (Worst Imaginable) *Severely limits how much you can eat*
	Abdominal pain or discomfort	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable) *Severe enough to require medications*
	Inactivity	Examples	0 (Absent) 1 2 3 *limited only with strenuous exercise*	4 5 6 7 *Even simple walking is a difficult task*	8 9 10 (Worst Imaginable) *Mostly chair or bed ridden*
	Cough	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable) *Severe enough to require medications*
Other patient reported symptoms derived from an international patient survey	Night Sweats	Examples	0 (Absent) 1 2 3 *Noticeable but do not need to change garment or sheets*	4 5 6 7 *Garment change but able to sleep*	8 9 10 (Worst Imaginable) *Garment change and interferes with sleep*
	Itching (pruritus)	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable) *Severe enough to require medications*
	Bone Pain (diffuse not joint pain or arthritis)	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable) *Severe enough to require medications*
	Documented fever at least once a week?	Yes or No If yes, state the actual temperature range:_____C or F			
	Unintentional weight loss (i.e. not the result of planned weight loss such as diet +/- exercise) in the last 6 months in excess of 10 pounds?	Yes or No If yes, state how many pounds lost last 6 months:_____			
	What is your Overall Quality of Life?	0 (As good as it can be) 1 2 3 4 5 6 7 8 9 10 (As Bad as it can be)			

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 7 for a listing of expected adverse events associated with the study agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Related – There is reasonable evidence that the AE is related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

Each participating investigator is required to abide by the reporting requirements. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the PI of this study, Dr. Desai, and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Principal Investigator, Dr. Desai, on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and related with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the Principal Investigator Dr. Desai within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Dr. Pinkal Desai
c/o
Jill Kleczko jmk2008@med.cornell.edu

435 E 70 St
Room 4F
New York, NY 10021
212-746-0284

The participating investigator must provide follow-up information on the serious adverse event as soon as possible. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Principal Investigator Dr. Pinkal Desai on the toxicity Case Report Forms.

11.5 Reporting to the Institutional Review Board (IRB)

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Dr. Pinkal Desai
c/o Jill Kleczko jmk2008@med.cornell.edu

435 E 70 St
Room 4F
New York, NY 10021

The Principal Investigator Dr. Desai will submit SAE reports from outside institutions, if applicable, to the Cornell IRB per their policies and procedures in reporting adverse events.

11.6 Reporting to the Food and Drug Administration (FDA)

The Principal Investigator Dr. Desai, as holder of the IND, will be responsible for all communication with the FDA. Dr. Desai will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and related to the study treatment (Suspected Unexpected Serious Adverse Reactions or SUSARs) according the regulatory-defined timelines (7-day or 15-day reports). Dr. Desai will copy Astex pharmaceuticals (SGI-110 manufacturer) on any such reports.

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. All IND annual reports will be submitted to the FDA by the IND Sponsor.

Events will be reported to the FDA using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

7 Calendar-Day Telephone or Fax Report:
The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301- 796-9845) to the FDA within 7 calendar days of first learning of the event.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports. Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event.

11.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating

investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at Cornell by Dr. Pinkal Desai and externally by the Cornell CRO QA Office and the Coordinating Center in accordance with the Cornell Data Safety Monitoring Plan. All trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at Cornell. Authorized representatives of the Coordinating Center may visit the site to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

12.1.2 Dr. Desai will be holding the IND for this study. She will comply with all regulated reporting requirements to the FDA.

Weill Cornell Medical College requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency. The WCMC Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, informed consent documents, and data and safety monitoring plan prior to study initiation. After the first fifteen patients have been treated and observed for 28 days, the DSMB will perform an initial safety analysis. After the initial safety analysis period, the DSMB will review the cumulative study data semiannually to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. Due to the nature of the underlying diseases of the subjects on this study and the prolonged duration of therapy that

may be required in order to observe clinical benefit with the proposed treatment, there will be no assessment of efficacy until at least 25 patients have been treated for at least 4 cycles of therapy. If, at that point, there are fewer than 10% responses, as defined in the protocol, the study will be stopped for futility. The WCMC DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCMC DSMB to address.

Stopping criteria also include:

- The early death of more than three of the first ten subjects, as defined by death within 28 days of beginning therapy.
- If there is an unacceptable rate of Grade 4 toxicities, as judged by the investigation team, study sponsor, or the WCMC DSMB.

The study PI will submit all written DSMB recommendations to the IRB upon receipt.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
  link does not work, error message

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

    - Title 21 Part 312 – Investigational New Drug Application
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Data Collection

Data will be collected and reported on either paper case report forms (CRF) or through an internal data monitoring system, which will be determined prior to the start of the study.

14. STATISTICAL CONSIDERATIONS

The hypothesis of this study is that SGI-110, a demethylating agent, will lead to at least a 25% response rate in any one or more of the following response assessments: IWG-MDS, IWG-MF criteria or MF-SAF scores. Based on historical data, there is approximately a 10% hematological response rate with standard therapies and there is no precedent for quality of life response with any current therapy

14.1 Study Design/Endpoints

This is an open-label, single-arm phase II study designed to explore the clinical activity of SGI-110, a demethylating agent, in patients with MPN. The hypothesis of this study is that SGI-110 will lead to at least a 25% response rate in any one or more of the following response assessments: IWG-MDS, IWG-MF criteria, or MF-SAF scores. Based on historical data, there is approximately a 10% hematological response rate with standard therapies and there is no precedent for quality of life response with any current therapy.

Sample size considerations:

This is a phase II trial with 50 patients in the study arm; a 95% confidence interval for the hematological response rate can be constructed to be within ± 12.0% of the observed response rate. This calculation assumes a hematological response rate of 25%. The primary endpoint is the hematological response proportion, as measured by any one or more of the following response assessments: IWG-MDS, IWG-MF criteria or MF-SAF scores. Based on historical data, the hematological response proportion based on standard therapies is approximately 10%. Sample size recommendations for the current design are determined according to A'Hern's exact single-stage phase II design (A'Hern, RP, 2001). We project a hematological response proportion of 10%, below which the regimen will be unacceptable, and a hematological response proportion of 25%, above which the regimen will be considered worthy of further exploration. The null hypothesis that the hematological response proportion is less than or equal to 10% will be tested against the alternative hypothesis that the hematological response proportion is greater than or equal to 25%. The sample size computations were performed assuming a 5% level of significance and 85% power. Patients will be continuously accrued throughout the study up to a maximum of 47 patients. The new regimen will be declared effective and worthy of further testing if 9 or more patients respond among the 47 patients entered into the study. This exact single-stage design yields a ≥ 0.85 probability of a positive result if the true hematological response proportion is $\geq 25\%$. It yields a ≥ 0.95 probability of a negative result if the true hematological response proportion is $\leq 10\%$. A one-sided 95% confidence interval constructed around the expected hematological response proportion of 25% will extend 10.4% from the observed hematological response proportion. Assuming that approximately 5% of patients will be unevaluable/ineligible, we anticipate that a total of 50 patients will be enrolled in the study (Reference: A'Hern AP. Sample size tables for exact single-stage phase II designs. Statistics in Medicine 2001;20:859-866.)

Analysis Plan:

The primary endpoint of the hematological response proportion will be calculated and a 95% confidence interval will be estimated via binomial proportions. Descriptive statistics will be utilized to describe the parameter proportion defined above (i.e., frequency, percent). Estimated differences in the hematological response proportion between categories of demographic and treatment variables of interest (evaluated by the two-sample t-test, Wilcoxon rank-sum test, Fisher's exact test, and chi-square test, as appropriate) will serve as preliminary data (i.e., hypothesis-generating) for future studies. Similar analyses will be conducted for secondary outcomes of quality of life. Exploratory analyses of the hematological response rate and quality of life outcomes will be also be stratified by specific cytogenetic and/or molecular subgroups of MPN.

All p-values will be one-sided with statistical significance evaluated at the 0.05 alpha level. One-sided ninety-five percent confidence intervals will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.3 (SAS Institute, Inc., Cary, NC) and Stata Version 13.0 (StataCorp, College Station, TX).

Safety Analyses:

The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

14.2 Reporting and Exclusions

14.2.1 **Evaluation of toxicity.** All participants will be evaluable for toxicity from the time of their first treatment.

14.2.2 **Evaluation of response.** All participants included in the study must be assessed for response to treatment. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

15. REFERENCES

1. Yoo, C.B., et al., *Delivery of 5-aza-2'-deoxycytidine to cells using oligodeoxynucleotides.* Cancer Res, 2007. **67**(13): p. 6400-8.
2. Chuang, J.C., et al., *S110, a 5-Aza-2'-deoxycytidine-containing dinucleotide, is an effective DNA methylation inhibitor in vivo and can reduce tumor growth.* Mol Cancer Ther, 2010. **9**(5): p. 1443-50.
3. Dinardo, C.D., et al., *Myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN, U): natural history and clinical outcome by treatment strategy.* Leukemia, 2014.
4. Mesa, R.A., et al., *The Myelofibrosis Symptom Assessment Form (MFSAF): an evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis.* Leuk Res, 2009. **33**(9): p. 1199-203.
5. Arber, D.A., et al., *The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia.* Blood, 2016. 127(20): p. 2391-2405.